REMARKS

Favorable consideration of this application is respectfully requested in view of the above amendment and following remarks.

Claims 28-46 and 48-55 are pending in the application. Claims 40, 43, and 50-54 have been withdrawn. Claims 28-39, 41, 42, 44-46, 48, 49 and 55 have been rejected. New claims 56-63 have been added. Support for the language in claims 56-63 can be found in the specification, e.g., page 4, lines 3-6 and lines 13-14 and page 8, lines 4-7. No new matter has been added.

At the outset, the Examiner indicated that he did not consider the Eggen reference (Chimica Oggi/Chemistry Today 23, pp. 21-24) listed in the information disclosure statement (IDS) because the year of this reference was missing. In response, a supplemental IDS is attached hereto which lists this reference including the year. In view of this correction, Applicants respectfully request that the Examiner consider this reference.

Claims 28, 30, 31, 36, 41, 42, 44-46, 49 and 55 have been rejected under 35 U.S.C. §102(b) as being unpatentable by Carpino et al., (J. Org. Chem. 1999, 64, 4324-4338, referred herein as Carpino et al.) as allegedly evidenced by Solomons et al., (Organic Chemistry Fifth Edition. New York: John Wiley & Sons, 1992, page 94, Table 3.1) and Lide (CRC Handbook of Chemistry and Physics, ed. DA Lide, 85th Edn., CRC Press, Cleveland OH, 2004-2005, web page 1.) In particular, the Examiner states *inter alia*:

> Carpino et al. also disclose at least one step (b), referred to as step (b'), in which an amine comprising a free anion or a latent anion is used as a scavenger of residual activated carboxylic acid (e.g., see page 4329, column 1, first paragraph wherein "ethanolamine" is disclosed). The reference does not state that ethanolamine possesses a "free anion or latent anion", but the examiner contends that this would be an inherent property of ethanolamine via the following equilibrium in water $NH_2CH_2CH_2OH \leftrightarrow NH_2CH_2CH_2O^- + H+$) (e.g., see Lide, web page 1, "Dissociation Constants of Organic Acids and Bases" section, Ethanolamine entry wherein pKa =9.5; see also Solomons, page 94, Table 1, wherein pKa of water = 15.74)"When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not."....
>
> ....[4] Applicants argue, "It is further asserted that Carpino et al. fail to teach one skilled in the art that the alcohol moiety of the ethanolamide function

> is an anion that can be used as a scavenger. Instead, Carpino et al. teach that the alcohol moiety of the ethanolamide function remains intact during aqueous washing and does not form an anion. This assertion is underlined by the fact that extractions within the Carpino protocol are performed at neutral pH corresponding to a dissociation extent of the ethanolamide function of 10^{-7}%. Accordingly, the ethanolamide function in the presence of aqueous washings as is described in Carpino et al. would not function as a scavenger as is recited"...
>
> [4] Again, Applicants assertion that only ethanolamide exists is entirely unsubstantiated (see [2] above). However, even if we assume, for the sake of argument, that only ethanolamide exists and that it only remains at a concentration of 10^{-7}[%]in its "anionic" form, that anion would still anticipate the claims because a person of skill in the art would expect that anion to scavenge just the same as any other anion albeit to an extent that is proportional to its decreased concentration. That is, Applicants' arguments are not commensurate in scope with the claims because Applicants do not set forth a "bottom limit" to the amount of scavenging that need occur...

Applicants respectfully disagree with the Examiner's assertions and conclusion and submit that independent claim 28 is not anticipated by Carpino et al. as allegedly evidenced by Solomons and Lide.

Applicants assert that Carpino et al. does not constitute an anticipatory reference. To this end, it is well established that to constitute an anticipatory reference the prior art must contain an enabling disclosure. It is respectfully submitted that the Carpino et al. reference does not contain an enabling disclosure of an amine comprising a free anion that can be used as a scavenger of residual activated carboxylic acid functions within the scope of the present invention.

As stated in the previous response, Carpino et al., with respect to utilizing ethanolamine, describe aqueous extractions, i.e., at neutral pH. At a neutral pH, an equilibrium of $NH_2CH_2CH_2OH \leftrightarrow NH_2CH_2CH_2O^-$ would shift to the left and the alcohol moiety of ethanolamine would dissociate only to the extent of 10^{-7}% and thus the alcohol moiety would essentially remain intact following the protocol of Carpino. The Examiner states that such an anion would still anticipate the claims because a person of skill in the art would expect that anion to scavenge just the same as any other anion albeit to an extent that is proportional to its decreased concentration. However, since only 10^{-7}% of the quenched compound, H-AA_2-NH-CH_2-CH_2-OH, would be deprotonated at a neutral pH, only 10^{-7}% deprotonated, quenched

compound could be removed during an extraction step. In essence, one skilled in the art utilizing the described extraction conditions of Carpino, even after performing hundreds of extractions would not be able to effectively remove the deprotonated, quenched compound, e.g., to a level below 1%. Accordingly, removal of the quenched compound in a deprotonated form would be practically impossible. Thus, the purported use of ethanolamine as a scavenger containing an anion-forming moiety in the Carpino protocol would not work to remove deprotonated, quenched compound and avoid formation of insertion sequences.

Further, Applicants respectfully draw the Examiner's attention to the fact that the argument described on page 9, last paragraph, of the Office Action dated January 25, 2007, is not in agreement with the process of the present invention. It is not the anion that is required for the scavenging process. The actual scavenging function in the scavenging compound of the present invention is an uncharged nucleophilic moiety (*i.e.*, an amine). The deprotonation of the anion-forming moiety takes place at a later stage of the synthesis cycle. This will be explained in more detail below.

As mentioned in the response dated January 20, 2006, after completion of a coupling within the scope of the present invention, residual activated carboxylic compound is scavenged with a compound containing both a nucleophilic moiety (*i.e.*, an amine) and an anion-forming moiety. The function of the nucleophilic moiety is to inactivate the residual activated carboxylic compound. This reaction is the actual scavenging process step. The anion-forming moiety is present in the scavenging compound as such ("free anion") or is present in a latent form which requires a deprotection step to yield the "free anion" (*e.g.*, carboxylate, sulphonate or phosphonate). This "free anion" has to be deprotonated under mildly basic aqueous conditions compatible with peptide synthesis. At this stage the scavenged compound is negatively charged and as such completely soluble in the aqueous phase. This aqueous phase is used to actively extract the scavenged compound (in the anionic form) from the reaction mixture and thus separate it quantitatively from the main reaction product (*i.e.*, the growing peptide chain). This is required in order to avoid the formation of insertion sequences in the next cycle of the synthesis. This process is schematically presented in the left part of Annex 1.

It is known to a person skilled in the art, that peptide synthesis is not compatible with strongly basic (aqueous) conditions, which would result in not merely destruction of the peptide, but also of the preferred solvent of the present invention (ethyl acetate). The pH value during peptide synthesis should therefore not exceed a pH value of approximately 12. As is evident from the left part of Annex 1, the scavenged compound (Z-AA_2-βAla-OBzl) resulting from scavenging with benzyl β-alaninate (a scavenging compound within the scope of the present invention) is deprotected to a carboxylic acid (H-AA_2-βAla-OH) and then completely deprotonated under the mildly basic conditions of the following extraction step (H-AA_2-βAla-O^-). In this anionic form it is completely removed from the reaction mixture resulting in a pure product solution at the end of a synthesis cycle.

Carpino et al. uses ethanolamine in the synthesis of peptides. For the sake of completeness a reaction scheme is provided on the right side of Annex 1 wherein ethanolamine replaces the scavenging agent of the present invention. Please note that the process on the right side of Annex 1 does **not** represent the process described by Carpino et al. As mentioned before, the conditions in peptide synthesis should not exceed a pH value of approx. 12 (*i.e*, mildly basic conditions). The scavenged compound (Z-AA_2-NH-CH_2 CH_2-OH) resulting from scavenging with ethanolamine upon deprotection (H-AA_2-NH-CH_2 CH_2-OH) is merely deprotonated to a small extent under these mildly basic conditions of the following extraction step (H-AA_2-NH-CH_2 CH_2-O^-). Although the reference cited by the Examiner (STN Express) provides merely a predicted value for the deprotonation of –OH of ethanolamine, *i.e.* a pKa of 12.87, for the sake of argument applicant will use this value as well. As calculated by the Examiner, at a pH of 12 ethanolamine would be deprotonated to an extent of approx. 11%. Consequently after one extraction step under mildly basic conditions it is removed from the reaction mixture in small amounts. Complete removal of H-AA_2-NH-CH_2 CH_2-OH in anionic form (H-AA_2-NH-CH_2 CH_2-O^-) under mildly basic conditions can only be achieved performing a multitude of mildly basic extractions. Applicant has calculated that 40 extraction steps are required to reduce the amount of quenched compound in the reaction mixture to a level below 1%. This implies a very inefficient, laborious and lengthy process. As a result of the lengthy exposure to basic conditions (even if they are relatively mild), the risk of degradation of the peptide and the applied solvent is

substantial. Reduction of the number of necessary extractions would in such case only be possible by performing the extractions at strongly basic pH, which is not desirable considering the stability of the peptide and solvent. Incomplete removal of the quenched compound results in an impure product solution at the end of the actual synthesis cycle and would lead to the formation of further impurities in the next synthesis cycle. Accordingly, it may be concluded therefore that ethanolamine utilized at mildly basic conditions, i.e., that is below pH 12, cannot be regarded as a scavenger containing an anion-forming moiety within the scope of the present invention.

In view of the above, withdrawal of the rejection of claims 28, 30, 31, 36, 41, 42, 44-46, 49 and 55 under 35 U.S.C. §102(b) is respectfully requested.

Claims 28-31, 36, 41, 42, 44-46, 48, 49 and 55 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Carpino et al., WO 00/71569 (Tolle et al.) and Houghten et al., Nature 1991, 354, 84-86 (Houghten et al.). Applicants respectfully disagree with the Examiner's conclusion and submit that the combination of references does not make obvious independent claim 28.

The argument proffered above to address the §102 rejection apply equally well to this rejection, namely that the purported use of ethanolamine as a scavenger containing an anion-forming moiety and aqueous extractions, i.e., neutral pH, as described in Carpino would not work to effectively remove deprotonated, quenched compound and avoid formation of insertion sequences.

Further, even at mild basic conditions, the use of ethanolamine as a scavenger would require the use of numerous extractions, which would in turn, result in the destruction of the peptide. Neither Tolle et al. nor Houghten et al. describe an amine comprising a free anion or latent anion that could function as a scavenger within the scope of the present invention, and thus Tolle et al. and Houghten et al. do not remedy the deficiencies present in Carpino et al.

In view of the above, withdrawal of the rejection of claims 28-31, 36, 41, 42, 44-46, 48, 49 and 55 under 35 U.S.C. §103(a) is respectfully requested.

Claims 28-39, 41, 42, 44-46, 48, 49, 51, 52 and 55 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-51 of copending Application No. 10/692,354.

In response, Applicants will address the obviousness-type double patenting rejection upon indication that claim 28 is deemed to be allowable except for the obviousness-type double patenting rejection.

A good faith effort has been made to place the present application in condition for allowance. If the Examiner believes a telephone conference would be of value, he is requested to call the undersigned at the number listed below.

Dated: May 25, 2007

Respectfully submitted,

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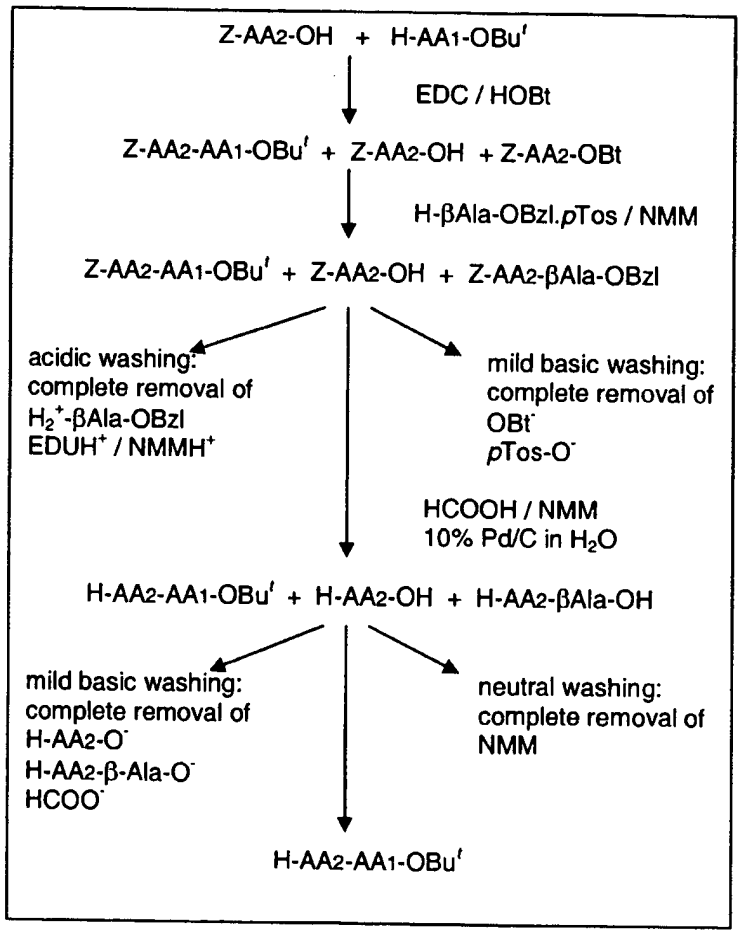
Attachment

ANNEX I

Process according to the invention
Including the preferred embodiment benzyl β-alaninate



A process comprising the steps of the present invention
Including ethanol amine used by Carpino et al.